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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/533,988	11/14/2005	Francesco Tisato	57708/400	2660

35743 7590 12/08/2006

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EXAMINER	
PERREIRA, MELISSA JEAN	
ART UNIT	**PAPER NUMBER**
1618	

DATE MAILED: 12/08/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/533,988	TISATO ET AL.	
	Examiner	Art Unit	
	Melissa Perreira	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 May 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,6-8 and 11-18* is/are rejected.

7)☐ Claim(s) *4,5,9 and 10* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/4/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Information Disclosure Statement

The information disclosure statements filed 5/4/05 contain minor informalities, such as the class and subclass is not listed for the foreign patent documents to be considered. The nonpatent literature reference listed contains the incorrect year of publication and does not list the relevant page numbers that are to be considered.

Specification

1. The disclosure is objected to because of the following informalities: The specification recites "3-hydroxythyramine" on p6 line 13. This is believed to be a spelling error and should read 3-hydroxytyramine. Appropriate correction is required.

Claim Objections

2. Claim 6 is objected to because of the following informalities: Claim 6 does not end in a period. Appropriate correction is required.

3. Claims 4 and 9 are objected to because of the following informalities: Claims 4 and 9 recite "3-hydroxythyramine". This is believed to be a spelling error and should read 3-hydroxytyramine. Appropriate correction is required.

Claim Rejections - 35 USC § 103

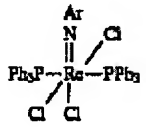
4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 1-3,6-8 and 11-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Archer et al. (5,589,576) in view of Duatti et al. (US 6,270,745).

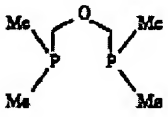
6. Archer et al. (5,589,576) discloses technetium imido radiopharmaceutical complexes I, Tc=NR, for use as radiodiagnostic and radiotherapeutic agents (column 1,

lines 6-12). The incorporation of a gamma-emitting nuclide provides for the diagnostic imaging with a gamma camera (column 1, lines 15-20). The formation of these radiopharmaceutical complexes occurs via substitution reactions on $[TcOX_5]^{2-}$ or $[TcX_6]^{2-}$ molecules. The rhenium compound (II, below) $[Re(NAr)Cl_3(PPH_3)_2]$ disclosed is known in the art (column 2, lines 15-20).



II

7. For the technetium imido complexes R may be aryl, $=NR^1R^2$ or substituted/unsubstituted alkyl (for example biologically active substituents. R^1 and R^2 may be H, aryl or substituted or unsubstituted alkyl, for example with N, O, S and/or P. Complexes may also comprise the formula, $L_nTc=NR$ where L_n is mono- or multi-dentate ligand (column 3), for example see III below (column 19; table 1).



III

8. The method of preparing the technetium imido radiopharmaceutical complexes, $L_nTc=NR$, first involves the preparation of the intermediate $[Tc=NR(Cl)_3(PPH_3)_2]$. This can be accomplished by the derivitization of technetium oxo-containing species by condensation with hydrazines (column 5, lines 13-16; column 10, lines 60+). Tc imido-complexes are generated by reaction of $[TcO_4]$ with hydrazine (derivatives), such as RCONHNHAR (1-phenyl-2-acetyl hydrazine; R = CH_3, Ph) in aqueous methanolic solutions with PPh_3 in the presence of concentrated HCl (column 9, lines 58-62; column 10, lines 42-44 and 60+; examples 4 and 6) followed by subsequent addition of the

ligand, L, for example III (above) (examples 5 and 6; column 19, table 1). Archer et al. (5,589,576) does not disclose the step of adding the electron-donating bidentate ligand containing the [N^-,S^-], [O^-,S^-], [S^-,S^-], [O^-,N^-], [N^-,N^-], [O^-,O^-].

9. Duatti et al. (US 6,270,745) discloses radioactive technetium nitride heterocomplexes, (Tc≡N)XY for use as radiopharmaceuticals for radiodiagnostic imaging or for radiotherapy (column 9, lines 3-4). X includes tridentate diphosphine compounds, such as IV (below) (column 3, lines 3-10) which encompass those of the instant claims:

IV

10. R^6 can be H, alkyl, substituted alkyl, aryl, a biologically active group, etc. (column 5, lines 3-6, 20 and 25-28). Bidentate ligand Y has a combination of two electron-donating atoms which are selected from O, S, N, such as [N^-,S^-], [O^-,S^-], [S^-,S^-], [O^-,N^-], [N^-,N^-], [O^-,O^-]. Some examples are thiosalicylic acid, ethylenediamine, phenylethylenediamine, etc. (column 6, lines 57+; column 7, lines 10 and 30). The method for preparing such technetium nitride heterocomplexes, (Tc≡N)XY involves reacting $^{99m}TcO_4^-$ with a hydrazine derivative and the tridentate diphosphine compound IV, X, in ethanol and aqueous hydrochloric acid solution, thus generating the intermediate $[(Tc{\equiv}N)X]_{int.}$ (column 7, lines 40-51 and 62; column 8, line 8; example 1). Under acidic conditions it can be speculated that the remaining coordination positions remaining after the coordination of the tridentate diphosphine compound are occupied by an unstable ligand, such as Cl^- (column 10, lines 21-26) giving a $[(Tc{\equiv}N)Cl_3(X)]_{int}$

derivative. It is believed that the intermediate $[(Tc{\equiv}N)Cl_3(X)]_{int}$ exists because in a more acidic environment a mixture of intermediates are formed by the coordination of Cl^-, OH^- with the coordination position remaining after the coordination of a diphosphine compound. Exchange reaction of the intermediate with the bidentate ligand, Y, involves adding tridentate diphosphine (X) compound IV and buffer solution to adjust the pH to 7 to 10, preferably about 8 (column 7, line 53; column 8, lines 24-29; examples 3 and 10). When adding the ligand Y to the intermediate it is important to use a buffer solution to adjust the pH to about 7 to about 10, more preferably 8 so that the exchange reaction can be more strictly controlled and an intermediate having a single geometry can be obtained. Pharmaceutical compositions of the technetium imido complexes were prepared by admixing the complexes with phosphate buffer and tween 80 (column 15, lines 63+).

11. At the time of the invention it would have been obvious to one ordinarily skilled in the art to utilize the Tc=N (technetium imido- functionality) to formulate radiopharmaceutical complexes for radiodiagnostic imaging and radiotherapy since these types of intermediates are known in the art. Archer et al. (5,589,576) discloses the preparation of the compound $L_nTc{=}NR$ via the $[Tc{=}NR(Cl)_3(PPH_3)_2]$ intermediate via substitution of the two monodentate PPH_3 ligands for the L_n tridentate ligand that encompasses the tridentate ligands of the instant claims. The steps for the method of preparation of the compound $L_nTc{=}NR$ (Archer et al.) encompass the steps for the method of preparation of the instant claims. Duatti et al. (US 6,270,745) describes the preparation of a similar $[(Tc{\equiv}N)Cl_3(X)]_{int}$ where X is a tridentate ligand that also

encompasses the tridentate ligands of the instant claims but further substitutes, via an exchange reaction, the $[(Tc{\equiv}N)Cl_3(X)]_{int}$ with a bidentate electron-donating ligand Y, such as ethylenediamine, thiosalicylic acid, etc.

12. Tc=N radiopharmaceutical complexes are also known for their ability to undergo various ligand substitution reactions. The method for preparing such technetium imido complexes containing Tc=NR, Tc-N=NR^1R^2 functionalities are compatible with the concomitant ligation of a wide variety of ligands substituted on N and coordinated to the technetium metal center. The biological characteristics of the technetium imido radiopharmaceutical complexes I, Tc=NR may be modulated by varying or altering the R substituent of the technetium imido- complex. Therefore it would have been obvious to alter the R substituent to improve the biological activity, such as site-specificity and uptake of the complexes and to experiment with the coordination of a variety of ligands to the Tc metal center. Duatti et al. discloses that the difference in biodistribution of the radiopharmaceutical complexes reflects the difference of the diphosphine compounds, thus it would be obvious to substitute a diphosphine ligand onto the technetium imido radiopharmaceutical complexes I, Tc=NR to tune the site-specificity to the desired organ. As disclosed above, the coordination of the bidentate electron-donating ligand, Y, as disclosed by Duatti et al. allows for the preparation of a radiopharmaceutical having a strictly controlled molecular structure without preparation of the optical or geometrical isomer. It would be obvious to substitute the tridentate diphosphine ligands and bidentate electron-donating ligands of Duatti et al. onto the Tc=NR complexes of

Archer et al.) to generate a single isomer that is site-specific to the desired location of the body of a patient for improved radiodiagnostic imaging and radiotherapy.

It is respectfully pointed out that instant claims 5,9,10 and 18 are product-by-process limitations. Even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process. In re Thorpe, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed Cir. 1985). See MPEP 2113.

Conclusion

No claims are allowed at this time. Claims 4,5,9 and 10 are not supported in the prior art. Claims 4,5,9 and 10 are objected to as being dependent upon a rejected base claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Melissa Perreira whose telephone number is 571-272-1354. The examiner can normally be reached on 9am-5pm M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mike Hartley can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

MP
November 16, 2006

MICHAEL G. HARTLEY
SUPERVISORY PATENT EXAMINER